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[Quarterly Journal of Medicine, Vol. 14, No. 56, July, 1921.]

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# THE LAW OF CARDIAC MUSCLE WITH SPECIAL REFERENCE TO CONDUCTION IN THE MAMMALIAN HEART[1]

By THOMAS LEWIS[2]

Present knowledge of conduction in the heart has come to us almost exclusively from work of the last few decades; latterly it has come more and more to mould our conceptions, not only of the normal heart-beat but of very many disorders of this beat as these are seen in sick men and women. If, by means of recent illustrations, we seek to show that medicine as a science rears itself still upon the science of physiology, no more apposite or convincing example could perhaps be found than the story of conduction in the heart, since its development from the masterly researches of Gaskell.

## *The Paths of Conduction.*

In recent years a structure termed the *sino-auricular node* has proved to be the tissue in which the mammalian heart originates its beat (1). It is from this structure, consisting of a meshwork of small muscle-cells and nerve elements, and lying at the mouth of the superior vena cava, that the contraction process is conducted to all parts of the heart. It is not proposed again to relate the evidence for this statement (2); that the conclusion is sound is now universally recognized. This node sets the rhythm of the normally beating heart, and is under intimate nervous control.

From it the wave of the contraction process passes in all available directions; the wave as a whole spreads concentrically in the muscle of the right auricle, passing up the superior cava against the blood-stream, down the taenia terminalis to the inferior cava, from base to tip of the right appendix, and across to the left auricle and appendix through the muscle-bands which unite the two chambers. It spreads also down the septum between the two auricles, and eventually involves the whole musculature of the auricle (3). It courses through the chief muscle-bands of the auricle in their length. These bands radiate from their point of concentration in the region of the *s.-a.* node. The arrangement is eminently suited to rapid distribution of the wave. It reaches the

[1] Abridged from the Linacre lecture delivered at Cambridge, May 6, 1921.

[2] Working on behalf of the Medical Research Council.

[Q. J. M., July, 1921.]

specialized structures which form in the mammal the union between the auricular and ventricular portions of the heart. Here it traverses the auriculo-ventricular node; this node is composed of very small interlacing fibres which, like those of the *s.-a.* node, are richly supplied by nerves. Next it passes through the bundle and its branches; it traverses these and thus arrives simultaneously at many points of the endocardial surface of the right and left ventricles. The fibres of the bundle branches, and in some species those of the bundle itself, are the largest in the heart; they are only locally striated, and possess very large and often multiple nuclei. They are called the fibres of Purkinje. Reaching the muscle of the ventricle, the wave penetrates this everywhere along lines which radiate from the centres of the two ventricular cavities, and terminates when it reaches the pericardial surface of the heart (4). Of these conclusions also we need have no doubt; the evidence is now too overwhelmingly in their favour. It is important to realize that any studies of conduction in the mammalian heart must take strict account of these anatomical paths. Further, it must be recognized at the beginning that the propagated wave, in its course from the *s.-a.* node to the ventricular pericardium, passes through fibres of varying architecture and constitution.

In its passage from the *s.-a.* node to the pericardial surface of the ventricle, the wave of the contraction process traverses muscular tissues of four types. These may be described in terms of relative size and of glycogen content.

*Size of fibre.* The largest striated fibres of the heart are the Purkinje cells; next to these stand the auricular fibres; the ventricular fibres are somewhat smaller;[3] smallest of the four are the fibres of the *a.-v.* node.

*Glycogen content.* Glycogen is held in greatest quantity in the Purkinje cells (5); these are laden. There is a good deal of glycogen in both the auricular and ventricular muscle, and it is said by those who have compared the two (6) that the auricle holds more than the ventricle. The *a.-v.* node holds little or no glycogen (7).

Thus the fibres through which the wave is conducted vary in their structure, they vary in their chemical constitution. Now, when we find tissues which differ in structure, we may be sure that differences in function will also be discovered; further, when we realize that hand in hand with these structural differences there are parallel differences of chemical constitution, we may anticipate with some confidence differences in function which are arranged in like order.

Having considered the size and the glycogen content of the striated fibres of the heart we place these fibres in their natural order, commencing with the fibres which are largest and richest in glycogen and ending with those which are smallest and poorest in glycogen. The order is as follows:

1. Purkinje fibre.
2. Auricular fibre.
3. Ventricular fibre.
4. Nodal fibre.

[3] The last difference is not emphatic.

We will now proceed to examine and compare the power of these four tissues to conduct.

*Rates of Conduction.*

Many observations have been undertaken upon rates of conduction in the heart muscle; many of the methods used have been faulty or subject to very appreciable error. That has been so because the paths of conduction have been recognized only recently, and no observations upon rate of conduction can be of value which do not take into account the path followed by the wave. The statements which follow apply to the dog's heart.

*In the auricle.* In the mammalian auricle the natural rate of conduction is estimated with precision by first ascertaining the exact starting-point of the wave and its lines of propagation, and by subsequently measuring the times of its arrival at points on these lines. That can be, and has been, done both for the excitation wave and the contraction wave which follows it (8). The rate is the same for both processes, and approaches the average figure of 800 mm. per second. The rate of propagation may also be ascertained by stimulating the auricle rhythmically in line with two points at which the times of arrival of the propagated waves are signalled. Values similar to those obtained for the natural wave are found (9).

*In the ventricle.* The mammalian ventricle offers peculiar difficulties, because the rates of conduction in the ventricular muscle and in the Purkinje substance, which lines its endocardial surface, are by no means the same. The method of chief value is to propagate waves artificially from the pericardial surface of the ventricle and in line with two points at which the arrival of the resultant waves is timed. Two precautions are essential to accuracy. The muscular wall must be of considerable thickness; for this reason the left ventricle is chosen; and the point of stimulation and points signalling the waves must be close together. Otherwise the rate of conduction obtained is not that of ventricular muscle, but is a rate comprised of that of ventricular muscle and Purkinje substance. The rates of both are measurable with considerable accuracy by adopting suitable methods; that of ventricular muscle averages 400 mm. per second, that of straight Purkinje fibres is approximately 4,000 mm. per second (10).

*In the a.-v. node.* A direct measure of conduction in the node is not possible; that conduction is slow is suspected from the delay between the contractions of auricle and ventricle, and from analogy with the fibres of the *a.-v.* ring of the frog. An estimate of actual conduction rate in the node may be obtained by considering certain transmission intervals.

In the naturally beating heart of medium-sized dogs the transmission interval from the *s.-a.* node to the septal muscle overlying the *a.-v.* node measures approximately 0·03 to 0·04 of a second. By a different method the interval to the *a.-v.* node itself is estimated at similar figures. We may take the mean 0·035 of a second as an estimate subject to no great error (11). The interval between the

starting of the wave and the appearance of R, the chief ventricular deflexion of the electro-cardiogram, is approximately 0·10 of a second (12) (see Fig. 1). The time lost between the arrival at the *a.-v.* node and the appearance of R, therefore, is approximately 0·065 of a second. Now R begins almost simultaneously with the arrival of the wave at the apex of the right ventricle, and if we subtract the time calculated for the wave to travel along the bundle-branches to the apex of

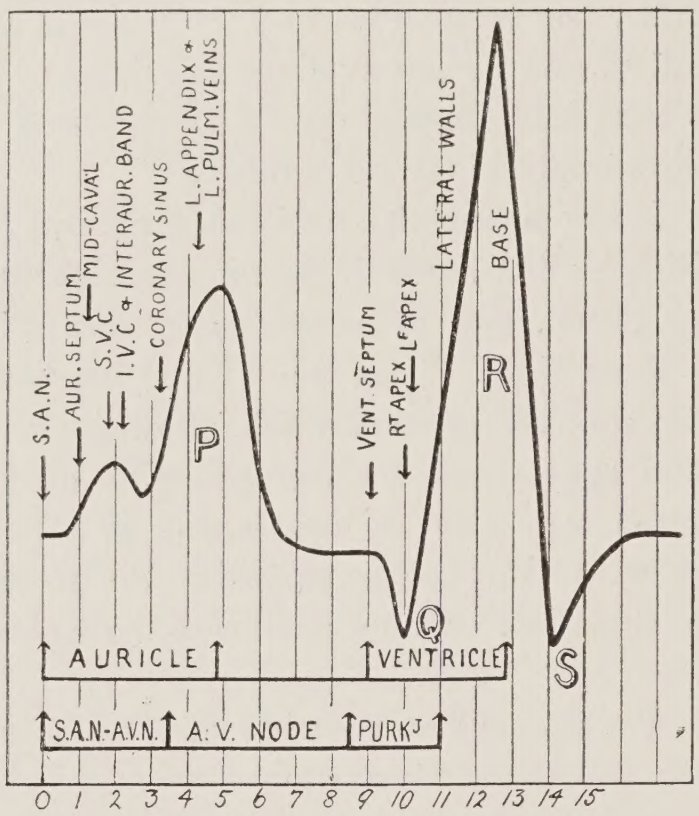


FIG. 1. An electro-cardiogram from a dog (P = auricular summit, and Q, R, and S = opening deflexions of the ventricular complex). The times at which the various parts of the muscle become active, or excited, relative to the deflexions of the electro-cardiogram are indicated above the curve on the basis of many direct observations. Below the curve, the periods during which the auricle and ventricle, each taken as a whole, become active are shown; and below this the periods during which the impulse is travelling from sino-auricular to auriculo-ventricular nodes through the *a.-v.* node and through the Purkinje system are indicated. The time lines are in hundredths of a second.

the right ventricle (on the basis of a conduction rate of 4,000 mm. per second this works out at approximately 0·01 to 0·015 of a second) we obtain a value of approximately 0·05 of a second for the passage of the node. Making an allowance for the distance traversed, let us say 10 mm. of tissue, the rate of conduction can scarcely be greater than 200 mm. per second; actually the rate is very probably somewhat less than is here stated.

To sum up, we have arrived at the following approximate figures:

| Tissue. | Rate of Conduction in mm. per sec. |
|---|---|
| 1. Purkinje substance | 4,000 |
| 2. Auricle | 800 |
| 3. Ventricle | 400 |
| 4. *A.-v.* node | 200 |

Now this is the order of the constituent fibre size, and it is the order of their

glycogen content. Our anticipation that structure and function would be found to march hand in hand is fulfilled in a remarkable manner. So striking is this example that I venture to propound the following law:

*The fundamental properties of muscle will be found to vary in their degree in the four types of cardiac fibre; if for any two types we can obtain a measure, then within reasonable limits we may predict the degree for the remaining two types by placing all four in their natural order.*

This law is propounded in the belief that it will lead us, if used circumspectly, to a closer understanding of many phenomena exhibited by the mammalian heart. In the mammalian heart the structures which possess the rhythmic property in highest degree are the *s.-a.*[4] and *a.-v.* nodes; they are alike constituted of fine muscle-fibres. The relative rhythmicity of the auricular and ventricular muscle and of the Purkinje fibres is not known; but it is known that all possess the function in lower degree than the nodes.

The law as I have stated it would lead us to anticipate that Purkinje fibres are the least rhythmic.

*The phenomenon of* 2:1 *response (half response).* We may now examine a curious but perfectly understood phenomenon, namely that of 2:1 response in cardiac muscle responding to extreme rates of stimulation. If the muscle of the mammalian auricle is stimulated at increasing rates, there comes a time when it will no longer respond to each stimulus. When this rate is reached, the auricle begins to respond to alternate impulses only. This condition of 2:1 response is due to the responsive phase of the cycle being brought to the vanishing point as diastole is reduced; alternate impulses fall on muscle which is still in the refractory state, which is still inexcitable; the critical rate at which this 2:1 response occurs may be taken as an index of the refractory period in heart muscle. Now the refractory period of auricular muscle is of shorter duration than is that of ventricular muscle, for its systole is shorter. Applying the law of cardiac muscle, we may predict that the duration of the refractory state in the muscle of the *a.-v.* node is longer than in either auricle or in ventricle. Recently this prediction has been put to the direct test, and it is found that the law holds good; the critical rate at which half response occurs in the auricular muscle is approximately 450 per minute; the critical rate for the *a.-v.* node lies with great regularity between 270 and 300 per minute; the critical rate for the ventricle is intermediate. Drive the auricle at rates surpassing 300 per minute and the ventricle will beat at a lower rate; but it is not the ventricle which fails to respond, for the ventricle will respond to each stimulus if these are directly applied to it; it is the *a.-v.* node which fails to transmit.[5] The *a.-v.* node is a natural blocking-point (13); it is a natural blocking-point because the length

[4] According to the law this node should be deficient in conducting power; very possibly the condition known as 'sino-auricular' block is due to retarded or inhibited escape of the wave from this node to the surrounding auricular tissue.

[5] Recent and unpublished observations with Dr. A. N. Drury and Dr. C. C. Iliescu.

of its refractory period is high.[6] This conclusion is cited to illustrate how the law of cardiac muscle may be used; in the first instance it was foretold that the critical rate for the *a.-v.* node would prove the lowest; it has been put to actual test and proves to be the lowest.

The law of cardiac muscle may be exemplified more fully in the accompanying table, in which the structure and constitution of the fibres are correlated with the more important properties of cardiac muscle. The order expressed in each vertical column is the order of decline in the characters or properties which are indicated in the head-lines of these columns. For the most part the order is based on actual observation; the bracketed figures are, however, theoretical; these are in the nature of predictions.

In as far as the predicted order is found in the future to obey the law, in so far will the view be confirmed that, on the one hand, the functions of the Purkinje fibres in general approach towards those displayed by nerve, while, on the other hand, the functions of nodal muscle approach towards those displayed by involuntary muscle. The last conception reminds us of the intimate control of involuntary muscle by the plexuses of Auerbach and Meissner; the intimate nervous control of the nodes of the heart may yet prove to be ordered upon a plan morphologically similar.

*The Law of Cardiac Muscle.*

| | Order of Decline. | | | | | | |
|---|---|---|---|---|---|---|---|
| Fibre. | Size. | Glycogen Content. | Conducting Power. | Absolute Ref. Per. | Rate of Recovery of Excitability. | Rhythmicity. | Contractile Power. |
| Purkinje | 1 | 1 | 1 | [4] | [1] | [4] | [4] |
| Auricular | 2 | 2 | 2 | 3 | [2] | [3] | [3] |
| Ventricular | 3 | 3 | 3 | 2 | [3] | 2 | [2] |
| Nodal | 4 | 4 | 4 | 1 | [4] | 1 | [1] |

The order denoted by bracketed figures is at present purely theoretical.

## *Altered Conduction.*

Although we may, for convenience, separately name several of the properties of cardiac muscle, it is not yet proven that these properties are independent functions in the sense which Engelmann would have led us believe. One of the seemingly most convincing cases which Engelmann made out was for the independence of the functions excitability and contractility (14). Recent observations (15) rob his chief evidence of its weight; the general trend of conclusion is opposed to the conclusion which he sought to establish. Engelmann was equally convinced of the independence of excitability and conductivity, though his argument for this conclusion was of a more speculative kind (16). This problem of the interdepen-

[6] To this is probably due the failure of interpolated extra-systoles of the ventricle to reach the auricle, a phenomenon which has hitherto remained mysterious.

dence or independence of excitability and conductivity has long been contended in the case of nerve; the compass has swung from one pole to the other. Similarly, in the case of muscle, opinion has swung to and fro; the case for interdependence has been emphasized of recent years by Straub (17) and Tait (18). Recent observations strongly support the last view. We may now summarize them, but, before doing so, it is to be pointed out briefly that nearly all the studies which concern themselves with altered conduction in the heart deal not with normal changes in the muscle but with changes which are essentially of a pathological kind. Of changed conduction in the heart beating under wholly natural conditions we have little exact knowledge;[7] such knowledge as we possess goes to show that conduction is relatively a very stable property, and that if changes in the rate of conduction do occur in the intact and healthy body such changes are uncommon or of very minor degree. This contention is one of some importance, for we are apt to forget that the conditions which we impose upon muscle experimentally, such as change of temperature, of pressure, of innervation, or of nutrition, conditions which provoke obvious defect in the conducting power of the muscle, are unnatural. Speaking of lowered conduction, to the neglect of possible minor changes, we may say that when conduction is altered by the means named the fibres of the muscle which is under observation are already verging on death. Thus, while we may be in a position to speak of conduction as a property of cardiac muscle, as yet we are scarcely warranted in regarding altered conduction as physiological.[8] Physiologically, as has been stated, conduction is stable; if conduction may be spoken of as a function of cardiac muscle, depressed conduction may not as yet be regarded as a normal event.

Having stated the belief that altered conduction, in so far as anything but very minor changes are concerned, is essentially pathological, that it is essentially a condition leading up to extinction of functions as a whole, the reasons may be stated for believing that the changes as we see them might reasonably be interpreted in terms of altered excitability.

*Heart-block as a result of raised rate.* The subject may be introduced by considering the reaction of the muscle to excessive rates of stimulation. If the muscle of the mammalian auricle is driven at rates which much surpass those occurring under natural conditions the speed at which the excitation wave is transmitted falls conspicuously. It falls progressively as the rate is advanced beyond a certain point. If the rate is advanced farther the phenomenon of 2 : 1 response is witnessed. We have recently obtained what appears to be convincing evidence[9] that the reduced rate of conduction from point to point and the 2 : 1 response, both of which occur as the rate of stimulation is advanced, are attributable to one and the same underlying cause. The very fact that the

[7] The most striking instance of physiological block has been found in hibernating bats by Miss Buchanan (*Proc. Physiol. Soc.*, 1911, xlii. 21).

[8] With perhaps the single exception named.

[9] The detailed evidence for the statements which follow is given by Lewis, Drury, and Bulger, *Heart*, Lond., 1921, viii.

last is always foreshadowed by the first as the rate rises at once suggests this relation. There is evidence that as the rate rises the fibres do not assume this halved rhythm simultaneously, but that one fibre after another is affected. When all [10] are affected 2 : 1 response of the muscle as a whole is seen ; when a proportion is affected the stimuli enter and travel through muscle, some fibres of which are in the responsive and some are in the refractory state. It is this *partially refractory* state of the muscle, as a whole, which is responsible for the increased delay in the waves' transmission from point to point. When a wave is transmitted through cardiac muscle, the course which it takes is not precisely a straight line ; the wave is travelling in a syncytial system of fibres, and these fibres are grouped in bands which are often waved or even interlacing. In following the shortest path which it can take, its track is consequently in

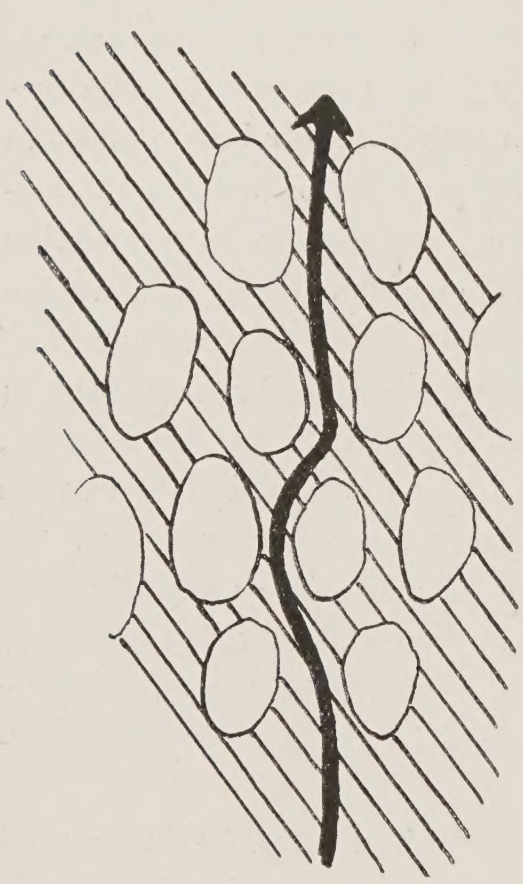

FIG. 2.

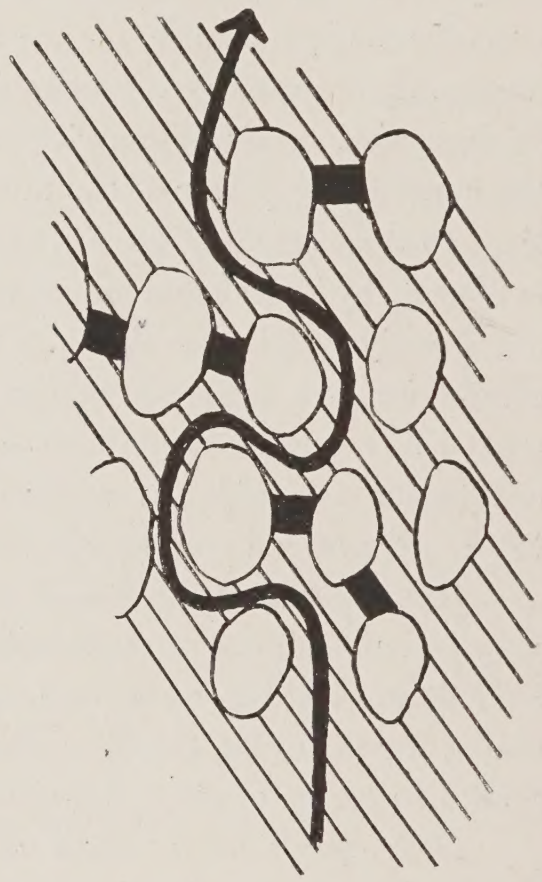

FIG. 3.

a measure sinuous (Fig. 2). Now suppose that the wave in its course through the responsive fibres encounters numerous fibres which are refractory ; its natural path is obstructed and the wave turns from side to side, may even turn back, before it finds a free channel of advance (Fig. 3). Briefly, the normal sinuosity of the path will increase in its degree ; the way will be longer, and the transmission rate from point to point will be reduced. We possess what we regard as proof that reduced speed of transmission, in response to unnaturally high rates of stimulation, is brought about in this way. It is known that the halved rhythm is due to alternate impulses falling upon muscle in which all the fibres are refractory ; we explain the reduced conduction rate which foreshadows it by supposing that the impulses enter muscle in which a proportion of the fibres are refractory.

[10] Or a sufficient number.

If our explanation is a correct one, then any influence which reduces the length of the refractory period should restore the rate of conduction to its original level; just as it should abolish the condition of 2 : 1 response. The most potent method of reducing the refractory period of auricular muscle is by vagus stimulation; this stimulation shortens systole, and with this shortening the refractory period falls. Vagus stimulation has precisely the effects anticipated. It abolishes the 2 : 1 response, it restores the rate of conduction to its natural level. Now this example is the more notable because we might have been led to suppose that vagal stimulation would reduce the rate of conduction, and because vagal stimulation is known to raise the threshold of excitability. Actually, the vagus has not the first effect; in the auricle it does not affect the rate of fibre conduction; this factor, therefore, need not be discussed. The raising of the threshold of excitability would act, if it acted at all, in a direction contrary to that which is observed. There can be no doubt, therefore, as to the meaning of the reaction, and no doubt as to the nature of the disturbed conduction. When the rate of auricular stimulation is advanced, then comes first a prolongation of the transmission intervals; then comes finally a failure of response, which is at first occasional, but which is eventually a 2 : 1 response. All these disturbances arise from the impulse entering, or the wave progressing through, muscle in which some or all of the fibres are refractory. Broadly speaking, the changes seen in an auricle which responds to high rates of stimulation are identical with those which characterize heart-block as this occurs at the *a.-v.* ring. That failure to respond may result from the relation of alternate impulses to the refractory period has been long recognized, but what has not been recognized hitherto, but has now been demonstrated, is that *prolongation of the transmission intervals* may arise in similar manner. This clear demonstration upon the muscle of the auricle obviously calls us to revise our ideas of heart-block as it is witnessed between the auricle and ventricle.

It has been stated already that 2 : 1 block is produced at the *a.-v.* ring by rapid stimulation of the auricle, and this block has been ascribed to similar causes, namely, to alternate impulses falling during the refractory period of the nodal muscle. This 2 : 1 response is foreshadowed, just as is the 2 : 1 response of the auricle itself, by prolonged transmission intervals. It can scarcely be doubted that they are attributable to a state of partial refractoriness, just as are the comparable prolongations in the auricular wall. But there is a serious difficulty; this form of heart-block at the node is not abolished by vagal stimulation, it is enhanced by it. The vagus is incapable of influencing fibre-conduction in the auricle, although it is known to exert a powerful control over this muscle. This being proved, an action of the vagus upon fibre-conduction in the node cannot be admitted, unless we are prepared to suppose that the vagus controls the properties of this node in a fashion fundamentally different from its control of auricular muscle. It is obviously impossible to assume that in comparable conditions disturbed transmission is due to one cause in the auricle and to a fundamentally distinct cause in the node. It would be most difficult to assume

that the vagus controls a hypothetical and independent property 'conduction' at the node, and fails to control it in the auricle. Although the vagus does not influence fibre-conduction in the auricle, it does ~~produce~~ effect prolonged transmission intervals and block in the auricular wall; *it abolishes both.* There is, therefore, in point of fact, a sharp contrast between the effects of vagal stimulation in the auricle and at the *a.-v.* junction, when it plays upon disorders of transmission invoked in these comparable ways. This contrast requires explanation, and the

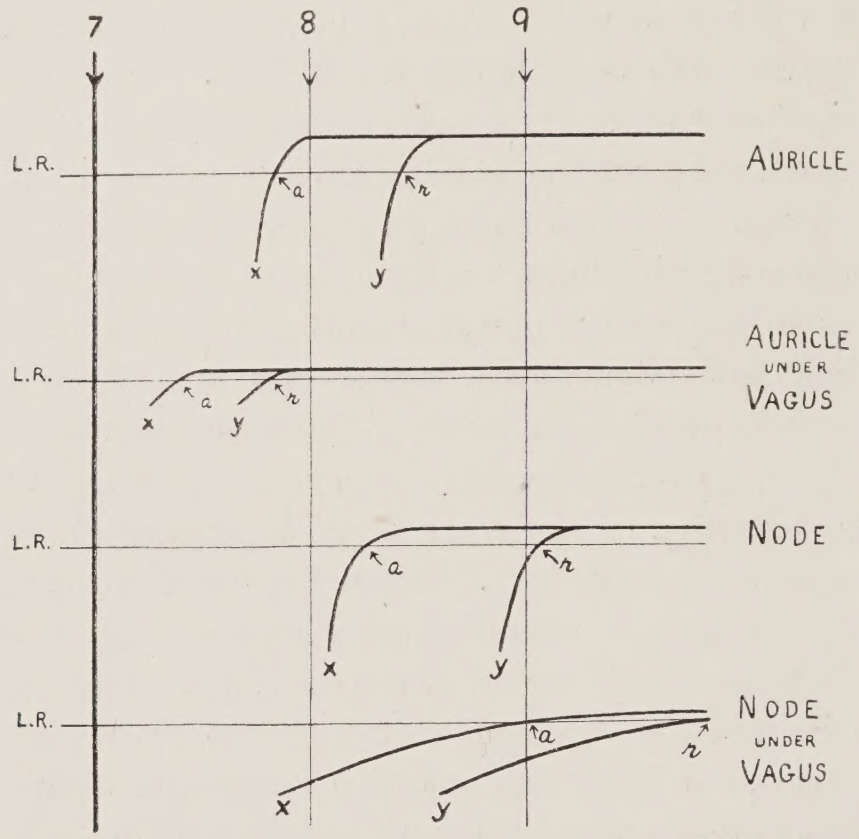


FIG. 4. A diagram illustrating the recovery of excitability on the basis of the hypothesis discussed in the text. The auricle is being stimulated by rapid rhythmic shocks, represented by the lines 7, 8, and 9. The muscle of the auricle responds to shock 7, and after its systole is complete its excitability recovers; the rate of recovery is rapid, but owing to the high rate of stimulation the fibres do not begin to recover simultaneously. Fibre *x* becomes responsive at *a*; this point marks the end of the absolute refractory period. Fibre *y* becomes responsive at *r*; this point represents the beginning of the wholly responsive stage. Period *a–r* represents the stage of partial refractoriness, and during this stimulus 8 falls on the muscle.

In the second line the auricle is under vagal stimulation. Although excitability recovers more slowly, yet, owing to recovery starting earlier, the wholly responsive stage is reached before stimulus 8 comes. Conduction in the auricle is therefore improved.

In the third line the nodal muscle is represented. The absolutely refractory period is long, and stimulus 8 falls within it; stimulus 9 falls in the phase of partial refractoriness. In these circumstances the node would respond to alternate stimuli.

In the fourth line the node is represented under vagal stimulation. It is supposed that while the absolutely refractory period is a little shortened, the rate at which excitability recovers is much reduced; consequently conduction is further depressed. The 9th stimulus is represented as falling just in the period of absolute refractoriness. L. R. = level of excitability necessary to yield response.

law of cardiac muscle brings us, so it is believed, to an understanding of the difference and enables us to adopt an explanation which, though it is still hypothetical, avoids the serious difficulties of the alternative explanations discussed. According to the law, the same properties of cardiac muscle are held by the different tissues in different degrees; we may assume with some measure of confidence that a given property will be affected differently by nerve control according to the order of

tissue upon which the nerve acts. According to our law, and according to observations first suggested by this law, the refractory period in the node is longer than in the auricle. We may not assume that the vagus fails to influence the duration of the node's refractory period, but may we not assume that vagal stimulation, while it is known profoundly to influence the length of the refractory phase in the auricle, has not a proportionate effect upon its length in the node? That would help us to explain why the vagus will abolish defects of transmission arising out of the refractory period in the auricle, while it fails to abolish similar defects in the node. But under this assumption the reason why the block is much increased at the node, and is not increased in the auricle, would still remain not clear.

We conclude in the first instance that the block originally produced by excessive rate is in both regions conditioned by unrecovered excitability, and that failure to recover is caused by lack of sufficient time to recover. By stimulating the vagus and thus profoundly reducing the length of systole in the auricle, a sufficient time for recovery is allowed. But clearly the degree to which excitability recovers is influenced not only by the time factor, it is influenced also by *rate* of recovery. If this rate of recovery is slower in the case of the node than in the case of the auricle—and we are led to expect that this is so in that there are clear indications that the metabolic processes in the node are the slower—may we not assume that where it is already slow, it will be more effectively retarded by the vagus influence? Let these assumptions be granted, and we develop a hypothesis which, while concerning itself with excitability only, offers an adequate explanation of the phenomena witnessed in both regions. For whereas the major influence of the vagus will be exerted towards increasing the period of recovery (by shortening systole) in the case of the auricle, thus rendering it more excitable when the next impulse reaches it, in the case of the node the major influence will be exerted to delay the rate of recovery, thereby rendering it less excitable when the next impulse reaches it. Thus the end results would be opposed. We suppose the two influences, opposed as they are, to be manifested both in the auricle and in the node, but that in the case of the auricle the lengthened time of recovery overshadows the reduced rate of recovery, while in the case of the node the converse holds.[11]

If the vagus has the twofold influence suggested, then it would be anticipated that the effect, which is in general the minor one, and consequently overshadowed, might in special circumstances become distinct. This appears to be the case, for several curious, and at first sight discrepant, observations are on record. Thus in certain of Erlanger and Hirschfelder's experiments heart-block produced in the *a.-v. bundle* by compression was not increased by vagal stimulation, but seems

[11] When vagus stimulation produces prolonged transmission intervals from auricle to ventricle, rather than dropped beats, it is supposed that it does so because the excitability recovers to the level at which response is possible at different time instants in different fibres; and that, as in the case of prolonged intervals in the auricle, the result is sinuous movement and increase in the length of the path travelled.

actually to have been relieved (19). There are also Gaskell's observations upon his auricular bridge in the cold-blooded heart (20); in these experiments vagal stimulation sometimes, but by no means always, produced block.

*Heart-block by compression.* This well-known method of producing prolonged transmission intervals and failure of response is comparable with many instances of block produced by disease. Often such block is not to be described in terms of muscle property, but in terms of tissue destruction. The lesser grades of block are sufficiently explained by surmising a general depression of functional efficiency. To particularize, such block might be attributed in some instances to a decline in the rate at which excitability recovers; in others it is conceivable that increased tension, by invoking a more isometric form of contraction, prolongs the systolic period and so shortens the time allowed for recovery.

*Heart-block arising from poisons.* These varieties of heart-block are, perhaps, amongst the most interesting exhibited by the heart. The poisons which are known to produce altered conduction are now almost innumerable; a very large proportion of all poisons which act powerfully on the muscle will, in sufficient doses or in given circumstances, produce block. A few of the more conspicuous of these may be cited, namely, the products of asphyxia, the whole of the digitalis series, potassium chloride, aconitin, and all drugs exerting a powerfully stimulant effect on the vagus, such as pilocarpine and muscarine. All these drugs, when given in doses sufficient to produce block, bring the muscle near, if not actually, to death. All are known or suspected to raise the threshold of excitability; some are definitely known to reduce the period of recovery by prolonging systole; heart-block produced by each may be explained by changed excitability; the action being upon the refractory period or upon the rate of recovery. There is another series of poisons, of which atropin may be taken as a striking example, which, having only an exalting influence upon the heart's metabolism, may nevertheless hinder conduction. The relation of atropin to block is a curious one. Atropin hinders conduction in the auricle only when the auricle is responding to high rates of stimulation; that is so because it prolongs the refractory period. It has no effect on the rate of fibre conduction (21). The relation between manifested block and the rate at which the heart is beating is one which has suffered an unfortunate neglect. Enough has been said to make it clear that, although there is much for us yet to learn, our conception of these protoplasmic poisons tends to move in one direction, namely, to couple apparent defects of conduction with defects of excitability; in what measure these defects are to be attributed to delay in the starting of this property towards recovery (lengthened systolic period), and to what extent they are to be attributed to delay in the rate of recovery once this has begun, is for the future to decide in the instance of very many of the poisons named. Now much of what has been said in regard to poisons is frankly speculative; their action has been discussed chiefly with a view to pointing out that their effects may be explained without introducing conduction as an independent property.

To sum up, there is probably no example of altered transmission of which

we have sufficient knowledge to speak, whether such is produced by nerve influences, by temperature change, by pressure or poison, which may not be explained on the basis of depressed function as a whole ;[12] if we are asked to speak particularly in terms of the properties of cardiac muscle, then it is in terms of *excitability* that these changes are first to be interpreted. In so speaking, we must ever bear in mind the morphology of the tissues in which the defect is exhibited, remembering that the four types of tissue display their several properties in different degrees, according to the law of cardiac muscle which has been formulated.

[12] In the case of atropin the depression is confined to the period of diastolic rest, and only occurs at high rates of beating.

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# STUDIES IN THE METABOLISM OF RICKETS[1]

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## I. IS RICKETS DUE TO A DEFICIENT SUPPLY OF CALCIUM TO THE BONES?

### The Calcium Content of the Blood, Muscle, and Brain, in Experimental Rickets in Dogs.

An historical sketch of the more important investigations already recorded upon rickets prepared by one of us (L. F.) was published as an introduction to Miss Ferguson's Report to the Medical Research Committee, 'A Study of Social and Economic Factors in the Causation of Rickets', Special Report Series No. 20, 1918.

It is unnecessary to recapitulate this. It showed clearly that the etiology of the disease is no better understood now than when Glisson described it in the seventeenth century, in spite of all the work that has been accomplished since then.

As Albu and Neuberg (1) say, after a full consideration of the calcium metabolism in rickets and of the various theories which have been advanced as regards the nature of the disease, 'Die Geschichte der Rachitis ist . . . . . mit einer Fülle neuer Hypothesen aber wenigen Tatsachen bereichert worden'.

That rickets is not simply an impaired calcification of bone or an exaggerated decalcification, as so many consider it to be, is shown by its clinical features and by the nature of the pathological changes in the bones. The general malaise of the child, the profuse sweating, the intense muscular weakness and the tendency to the development of tetany, all indicate some general disturbance of which the bone changes are merely one manifestation, and any explanation of the nature of the disease must explain this group of symptoms.

Further, the pathology of the bone changes and the formation of the characteristic osteoid tissue mark it as a disease *sui generis*, totally different from conditions of a mere failure in calcification.

Since one of the most patent changes is the softening of the bones, great

[1] The expenses of these investigations were defrayed by the Medical Research Council, to which our thanks are due.

[2] Throughout this and the next part Noël Paton and Leonard Findlay are responsible for the general plan of the work, Noël Paton for the experimental and Leonard Findlay for the clinical part. J. Sharpe is responsible for the chemical analyses.